

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
23 October 2003 (23.10.2003)

PCT

(10) International Publication Number
WO 03/087082 A1

(51) International Patent Classification⁷: **C07D 311/10**

1551-14, Shillim 9-dong, Kwanak-ku, Seoul 151-019 (KR).

(21) International Application Number: PCT/KR02/00627

(22) International Filing Date: 9 April 2002 (09.04.2002)

(25) Filing Language: Korean

(26) Publication Language: English

(71) Applicant (for all designated States except US): **ELCOM BIOTECHNOLOGY, CO., LTD.** [KR/KR]; #1004, RiverHill Officetel, 127, Kwangjang-dong, Kwangjin-ku, Seoul 151-742 (KR).

(74) Agent: **CHOI, Kyu-Pal**; Halla Classic Building 4F, 824-11, Yeoksam-dong, Kangnam-ku, Seoul 135-080 (KR).

(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(72) Inventors; and

(75) Inventors/Applicants (for US only): **YOON, Jeong-Seon** [KR/KR]; 525, Ohyang 5-ri, Gamgok-myun, Eum-seong-gun, Chungcheongbuk-do 369-850 (KR). **LEE, Ji-Young** [KR/KR]; 1554-19, Shillim 9-dong, Kwanak-ku, Seoul 151-019 (KR). **KIM, Young-Choong** [KR/KR]; Walker Hill Apt. #51-302, Kwangjang-dong, Kwangjin-ku, Seoul 143-210 (KR). **LEE, Ki-Yong** [KR/KR]; Gongdan 3-dong Jugong Apt. #314-204, 256, Gongdan-dong, Kumi-shi, Kyungsangbuk-do 730-030 (KR). **SUNG, Sang-Hyun** [KR/KR]; #602, Daehakdang Building, 116-2, Shillim 2-dong, Kwanak-ku, Seoul 151-012 (KR). **KIM, Hak-Joong** [KR/KR]; Walker Hill Apt. #32-101, Kwangjang-dong, Kwangjin-ku, Seoul 143-210 (KR). **KANG, So-Young** [KR/KR]; 103,

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— with international search report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: **PYRANOCOUMARIN DERIVATIVES**

(57) Abstract: The present invention relates to compounds of the following formula (I) or pharmaceutically acceptable salts thereof. The present invention also relates to use for a cognitive-enhancing agent of compounds of the following formula (I) or pharmaceutically acceptable salts thereof and to a process for preparing the same. Further, the present invention relates to use for a cognitive-enhancing agent of decursin of the following formula (II) or pharmaceutically acceptable salts thereof. In addition, the present invention relates to extracts of *Angelica gigantis* Radix comprising decursin of the following formula (II), having cognitive-enhancing effects.

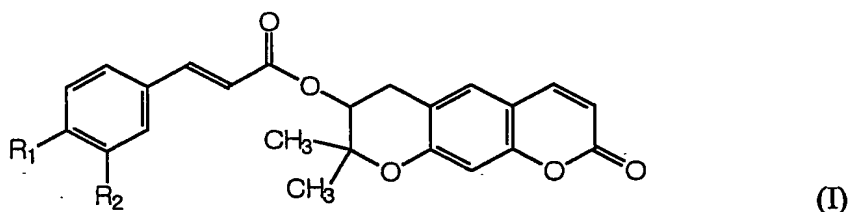


WO 03/087082 A1

PYRANOCOUMARIN DERIVATIVES

TECHNICAL FIELD

5 The present invention relates to pyranocoumarin derivatives having the following general formula:



, wherein R₁ and R₂ each represent hydrogen or C₁₋₄alkoxy, or pharmaceutically acceptable salts thereof.

10

BACKGROUND ART

15 Senile dementia has recently been recognized as a degenerative central nerve system disorder. The number of patients suffering from the disease has been increased to become a serious social problem, and so the prevention, amelioration, and treatment of the disease are now considered very important.

20 Alzheimer's disease, vascular diseases, Parkinson's disease, hypothyroidism, and alcoholic dementia are known as disorders which may cause dementia, but more than 50% of the patients suffering from senile dementia are found to suffer from Alzheimer's disease. The central nerve system of the patients suffering from Alzheimer's disease is generally impaired, and particularly, cholinergic neuron is most severely impaired. Thus, the studies to develop therapeutic agents to improve cholinergic neuronal functions have been
25 vigorously conducted.

A method to improve the functions of impaired cholinergic neuron is to administer cholinergic receptor agonist or acetylcholinesterase (AChE) inhibitor to inhibit degradation of acetylcholine (ACh), a cholinergic neurotransmitter, and thereby to maintain the concentration of synaptic ACh.

5

However, cholinergic receptor agonist has a disadvantage to be readily degraded *in vivo*, and thus, AChE inhibitor is generally used. That is, AChE inhibitor ameliorates the conditions of senile dementia by preventing the degradation of AChE by inhibiting the activity of AChE, an enzyme to degrade ACh, and maintaining the concentration of synaptic ACh, and thereby sustaining a series of cholinergic receptor-mediated reactions.

10

This is supported by the fact that most of the drugs that have been developed as therapeutic agents for Alzheimer's disease and currently on clinical use or trial are AChE inhibitors. AChE inhibitors that have been approved by the United States Food and Drug Administration and used as therapeutic agents of dementia are exemplified by tacrine (THA, Cognex®), donepezil (Aricept®), rivastigmine (Exelon®), and galanthamine (Reminyl®) that is most recently approved. However, these AChE inhibitors are known to have such problems as hepatotoxicity, short half-life, low bioavailability, etc. Thus, more studies have been performed to develop a novel AChE inhibitor.

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20

The present inventors have tested various natural products for AChE inhibitory activity to identify the activity with using *in vivo* experimental models by finding a substance with AChE inhibitory activity from the natural products that have been used as traditional Korean folk medicines for a long time. As a result, the present inventors found out that a methanolic extract of *Angelicae gigantis Radix* has significant AChE inhibitory activity and cognition-enhancing activity.

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Angelicae gigantis Radix is an herbal medicine used as a sedative, an analgesic, or a tonic agent, and particularly an essential drug used after childbirth for anemia and women's diseases, etc. by sedative and menstruation-promoting actions. In Korea, the

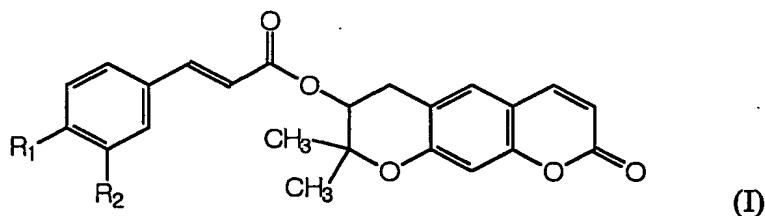
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dried root of *Angelica gigas* Nakai has been used as *Angelicae gigantis Radix*.

Further, the present inventors isolated and purified active ingredients showing AChE inhibitory and cognition-enhancing activities from *Angelicae gigantis Radix*, and synthesized many compounds by using the active ingredients as starting materials and tested them for their cognition-enhancing activity. As a result, they found out pyranocoumarin derivatives of the general formula (I) have cognition-enhancing activity. Therefore, the present inventors completed the present invention.

DISCLOSURE OF THE INVENTION

The present invention provides pyranocoumarin derivatives of the following general formula:



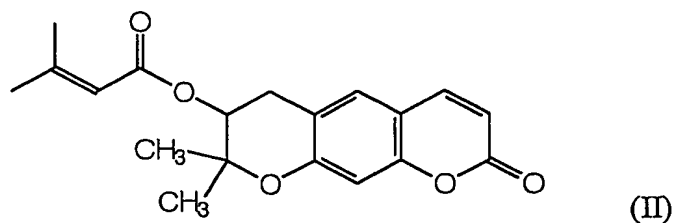
, wherein R_1 and R_2 each represent hydrogen or C_{1-4} alkoxy, or pharmaceutically acceptable salts thereof.

The present invention also provides an agent for enhancing cognition, comprising the compounds of the above general formula (I) or pharmaceutically acceptable salts thereof.

The present invention further provides a process for preparing the compounds of the above general formula (I).

The present invention still further provides an agent for enhancing cognition, comprising decursin of the following formula:

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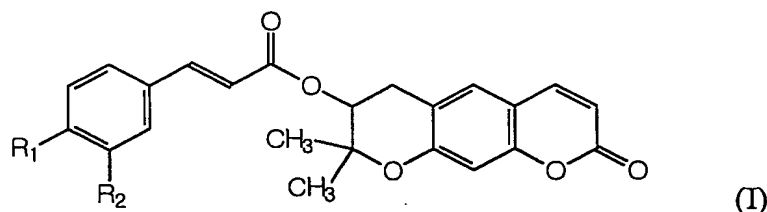


or a pharmaceutically acceptable salt thereof as an active ingredient.

The present invention still further provides an extract of *Angelicae gigantis Radix*,
 5 comprising decursin of the above formula (II).

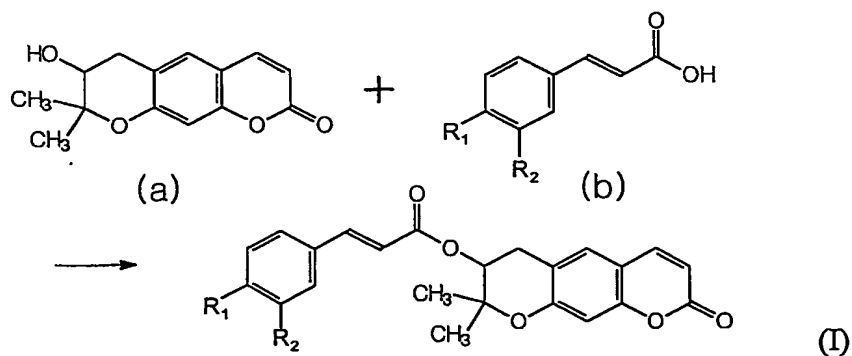
Hereinafter, the present invention will be explained in detail.

One aspect of the present invention provides novel compounds of the general
 10 formula:



, wherein R_1 and R_2 each represent hydrogen or C_{1-4} alkoxy, and preferably, R_1 is OCH_3 , and R_2 is hydrogen.

15 Another aspect of the present invention provides a process for preparing the compounds of the general formula (I) by conventional esterification reaction of decursinol (a) with phenyl propanoids (b), as depicted in the following reaction scheme:



The starting material, decursinol (a), may be prepared by direct extraction of *Angelicae gigantis Radix*, or by alkaline hydrolysis of decursin of the above formula (II), one ingredient of *Angelicae gigantis Radix*.

5 The present inventors first confirmed that decursin of formula (II), one ingredient of *Angelicae gigantis Radix*, has cognition-enhancing activity, synthesized many compounds using the ingredients of *Angelicae gigantis Radix* as starting materials, and screened the compounds for their cognition-enhancing activity. As a result, the present inventors found that the compounds of the general formula (I) have superior cognition-
10 enhancing activity.

A third aspect of the present invention provides an agent for enhancing cognition, comprising the compounds of the general formula (I) as an active ingredient.

15 The compounds of the general formula (I) according to the present invention can be formulated according to methods known in pharmaceutical field. The compounds alone or in admixture with pharmaceutically acceptable carriers, excipients, etc. are manufactured into conventional pharmaceutically acceptable dosage forms, for example, injectable formulations, solutions, syrups, tablets, capsules and the like. The compounds
20 of the general formula (I) according to the present invention may be converted into pharmaceutically acceptable inorganic or organic salts using conventional pharmaceutical methods. They may be administered by oral or parenteral route.

The dose of the compounds of the general formula (I) according to the present
25 invention may be appropriately selected depending upon absorption rate and excretion rate of the active ingredient, patient's age, body weight, sexuality and condition, and severity of disease to treat, and generally, their daily dose is in the range of 0.01 to 500 mg/kg, and preferably, 0.1 to 200 mg/kg to an adult. The compounds of formula (I) of the present invention may be administered several times with a regular interval, if necessary.

A fourth aspect of the present invention provides an agent for enhancing cognition, comprising decursin of the above formula (II) as an active ingredient.

Decursin of the present invention may be extracted from *Angelicae gigantis Radix*, or synthesized using conventional methods. One example of the extraction method of *Angelicae gigantis Radix* in the present invention is as follows.

The root of *Angelica gigas* Nakai is extracted with C₁₋₄alcohol, for example, methanol, ethanol, propanol, etc., and the obtained extract is suspended in water, and then, partitioned with dichloromethane (CH₂Cl₂) to obtain water fraction and dichloromethane fraction. The dichloromethane fraction is further purified by column chromatography on silica gel (for example, using n-hexane:CHCl₃:MeOH as an eluent), and recrystallized to obtain decursin.

The above extract of *Angelicae gigantis Radix* and decursin according to the present invention have excellent cognition-enhancing activity.

Decursin and extract of *Angelicae gigantis Radix* according to the present invention may be formulated according to methods known in pharmaceutical field, and decursin of the present invention may be converted into pharmaceutically acceptable inorganic or organic salts thereof according to conventional pharmaceutical methods.

Doses of decursin and *Angelica gigantis Radix* extract of the present invention are generally in the range of 0.01 to 500 mg/kg, and preferably, 0.1 to 200 mg/kg a day to an adult. The extract of *Angelicae gigantis Radix* according to the present invention may be administered at 0.01 to 500 mg once to three times a day, and decursin of the present invention may be administered at 0.1 to 200 mg once to three times a day.

As used herein, the term "*Angelicae gigantis Radix*" means the root of *Angelica gigas*, the term "C₁₋₄alcohol" means methanol, ethanol, propanol, isopropanol or butanol,

for example, and the term "C₁₋₄alkoxy" means methoxy, ethoxy, propoxy, isopropoxy or butoxy, for example.

BEST MODE FOR CARRYING OUT THE INVENTION

The present invention will be more specifically illustrated by the following examples. However, the following examples should not be construed to limit the scope of the present invention.

Example 1: Extraction and fractionation of Angelicae gigantis Radix

The dried root of *Angelica gigas* (5 kg) was finely powdered, and extracted with MeOH in an ultrasonic apparatus to obtain a methanolic extract (350 g). The extract was suspended in water, and partitioned with CH₂Cl₂ to obtain CH₂Cl₂ fraction (220 g).

Example 2: Isolation and structural identification of decursin from the extract of Angelicae gigantis Radix

The CH₂Cl₂ fraction of *Angelica gigas* obtained in Example 1 was subjected to column chromatography on silica gel (n-hexane: CHCl₃: MeOH) to obtain 7 fractions (AG-C-01 to 07). A part of AG-C-03 of those fractions was recrystallized with EtOH to isolate 678 mg of Compound 1. The compound emitted purple fluorescence at UV of long wavelength (365 nm), and developed purple color with anisaldehyde-H₂SO₄.

Compound 1:

Colorless prism

C₁₉H₂₀O₅

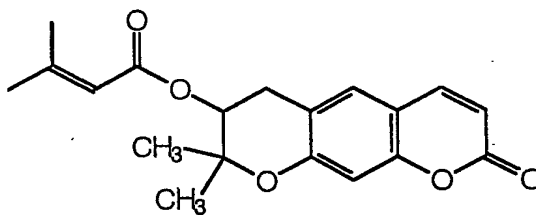
EIMS (*m/z*) (rel. int.): 328[M]⁺ (0.7), 228 (21.4), 213 (100.0), 83 (24.7), 55 (20.1)

¹H NMR (300MHz, CDCl₃): δ 1.31 (3H, *s*, CH₃-2'), 1.33 (3H, *s*, CH₃-2'), 1.83 (3H,

$d, J = 1.2$ Hz, $\text{CH}_3\text{-4''}$), 2.09 (3H, $d, J = 1.2$ Hz, $\text{CH}_3\text{-3''}$), 2.85 (1H, $dd, J = 4.9, 17.3$ Hz, H-4'), 3.18 (1H, $dd, J = 4.9, 17.3$ Hz, H-4'), 5.04 (1H, $t, J = 4.9$ Hz, H-3'), 5.61 (1H, m , H-2''), 6.19 (1H, $d, J = 9.5$ Hz, H-3), 6.74 (1H, s , H-5), 7.11 (1H, s , H-8), 7.56 (1H, $d, J = 9.5$ Hz, H-4) ppm

^{13}C NMR (75MHz, CDCl_3): δ 20.3 ($3''\text{-CH}_3$), 23.1 ($2'\text{-CH}_3$), 25.0 ($2'\text{-CH}_3$), 27.5 (C-4''), 27.9 (C-2'), 69.1 (C-4'), 76.6 (C-3'), 104.7 (C-8'), 112.8 (C-10'), 113.2 (C-3), 115.5 (C-2''), 115.9 (C-6), 128.6 (C-5), 143.1 (C-4), 154.1 (C-9), 156.4 (C-7), 158.5 (C-3''), 161.3 (C-2), 165.7 (C-1'')

Chemical formula:



Compound 1 was identified as decursin by comparing the above physicochemical properties and spectroscopic results with those in the literature (Ahn, K. S. et al. (1996) Decursin: A cytotoxic agent and protein kinase C activators from the root of *Angelica gigas*, *Planta Med.* 62: 7-9).

Example 3: Preparation of pyranocoumarin derivatives of the general formula (I)

(1) Alkaline hydrolysis of decursin

Decursin of 1 g obtained from Example 2 was dissolved in 40 ml of 5% ethanolic KOH, and a reaction was performed at 60 °C for 1 hour. The reaction mixture was cooled and thereto was added water to terminate the reaction. Then, the reaction mixture was partitioned with ethyl acetate. The fraction was concentrated and recrystallized with chloroform to obtain Compound 2 (680 mg).

Compound 2 emitted blue fluorescence at UV of long wavelength (365 nm), and

developed purple color with anisaldehyde-H₂SO₄.

Compound 2:

C₁₄H₁₄O₄

5 Colorless needles

EIMS (*m/z*) (rel. int.): 246 [M]⁺

¹H NMR (300MHz, CDCl₃): δ 1.34 (3H, *s*, gem-CH₃), 1.37 (3H, *s*, gem-CH₃), 2.81 (1H, *m*, H-4'), 3.09 (1H, *m*, H-4'), 3.85 (1H, *t*, *J* = 5.0 Hz, H-3'), 6.20 (1H, *d*, *J* = 9.5 Hz, H-3), 6.76 (1H, *s*, H-5), 7.16 (1H, *s*, H-8), 7.56 (1H, *d*, *J* = 9.5 Hz, H-4) ppm

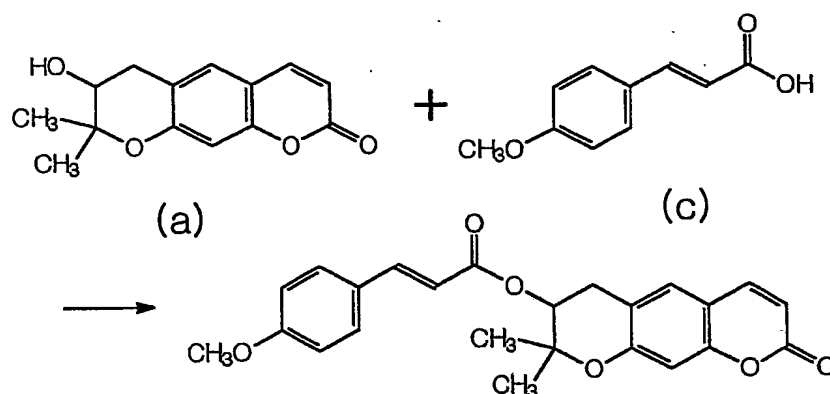
10 ¹³C NMR (75MHz, CDCl₃): δ 22.0 (gem-CH₃), 25.0 (gem-CH₃), 30.6 (C-2'), 69.1 (C-4'), 78.1 (C-3'), 104.7 (C-8), 112.9 (C-10), 113.3 (C-3'), 116.4 (C-6), 128.9 (C-5), 143.1 (C-4), 154.1 (C-9), 156.4 (C-7), 161.2 (C-2) ppm

Compound 2 was identified as decursinol by comparing the above
15 physicochemical properties and spectroscopic results with those in the literatures (Konoshima et al. (1968) Coumarins from the root of *Angelica gigas* Nakai. *Chem. Pharm. Bull.* 16: 1139-1140; and Seong et al. (1988) Studies on the constituents of the roots of *Angelica flaccida* Kommarov. *Kor. J. Pharmacogn.* 19: 233-238).

20 (2) Synthesis and isolation of Compound 3

As depicted in the following reaction scheme, Compound 2(a) obtained from the above (1) of 246 mg (1 mmol), p-methoxycinnamic acid (c) of 356 mg (2 mmol), and 4-(dimethylamino)-pyridine (DMAP) of 122 mg (1 mmol) were dissolved in 10 ml of
25 anhydrous dichloromethane, and a reaction was performed under nitrogen at room temperature for 5 minutes. Then, 1,3-dicyclohexyl carbodiimide (DCC) of 300 mg (1.5 mmol) was added thereto, and the reaction was further performed for 2 hours. The reaction mixture was cooled and filtered through Celite 545, and then, the filtrate was subjected to column chromatography on silica gel (hexene:ethyl acetate=2:1) to isolate
30 Compound 3 (250 mg).

10



(3) Structural identification of Compound 3

$C_{24}H_{22}O_6$

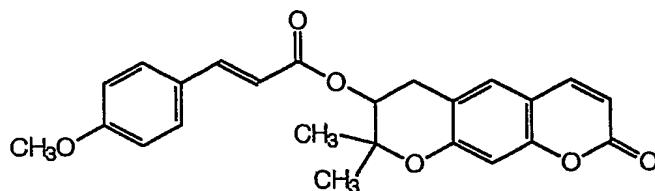
EMS (m/z): 406 $[M]^+$, 246 $[M-160]^+$

1H NMR (300MHz, CD_3OD): δ 1.28 (3H, s, gem- CH_3), 1.30 (3H, s, gem- CH_3), 2.84 (1H, *dd*, $J = 17.5, 4.6$ Hz, $H_{\alpha-4'}$), 3.18 (1H, *dd*, $J = 18.4, 4.6$ Hz, $H_{\beta-4'}$), 3.69 (3H, s, OCH_3), 3.99 (1H, *q*, $J = 7.1$ Hz, H-3'), 6.10 (1H, *d*, $J = 9.5$ Hz, H-3), 6.10 (1H, *d*, $J = 15.84$ Hz, H-7''), 6.64 (1H, *s*, H-5), 6.80 (2H, *d*, $J = 8.9$ Hz, H-3'', 5''), 7.24 (1H, *s*, H-8), 7.39 (2H, *d*, $J = 8.9$ Hz, H-2'', 6''), 7.50 (1H, *d*, $J = 15.84$ Hz, H-8''), 7.69 (1H, *d*, $J = 9.5$ Hz, H-4)

ppm

^{13}C NMR (75MHz, $CDCl_3$): δ 22.0 (gem- CH_3), 23.8 (gem- CH_3), 27.3 (C-2'), 54.4 (OCH_3), 70.0 (C-4'), 76.7 (C-3'), 103.6 (C-8), 112.1 (C-3), 112.9 (C-10), 114.0 (C-3'', 5''), 114.1 (C-7''), 116.3 (C-6), 126.7 (C-1''), 129.1 (C-5), 129.7 (C-4'', 6''), 144.1 (C-4), 145.4 (C-8''), 153.9 (C-9), 156.6 (C-7, 4''), 161.8 (C-2), 166.6 (C-9'') ppm

Chemical formula:



From the above physicochemical properties and spectroscopic results, Compound 3 was identified as 8,8-dimethyl-7-[3-(4-methoxyphenyl)-2*E*-propenoxy]-2*H*,6*H*-

benzoyl[1,2-*b*:5,4-*b'*]dipyran-2-one (IUPAC name; 3-(4-methoxyphenyl)-acrylic acid-2,2-dimethyl-8-oxo-3,4-dihydro-2*H*,8*H*-pyrano[3,2-*g*]cromen-3-yl ester).

Experiment 1: Activity test of Angelicae gigantis Radix extract

5

(1) Measurement of cholinesterase inhibitory activity

AChE inhibitory activity of the methanolic extract and CH₂Cl₂ fraction of *Angelica gigas* of the above Example 1 was measured by the method of Ellman et al. (Ellman, et al. (1961) A new and rapid colorimetric determination of acetylcholinesterase activity, Biochem. Pharmacol. 7: 88-95).

To a test tube containing a chromogen (5,5-dithiobis-2-nitrobenzoic acid) and a sample was added AChE homogenated with phosphate buffered saline (Electric eel Type V-S, Sigma), and a reaction was performed at 37 °C for 5 minutes, and thereto was added a substrate for the enzyme, acetylcholine iodide, and a reaction was further performed at 37 °C for 3 minutes. Neostigmine bromide was added thereto to terminate the reaction, and then, the absorbance was measured at 412 nm to obtain AChE inhibition (%). The above procedure was repeated with no AChE as a blank, or with no sample as a control.

The results are shown in the following Table 1.

Table 1 (concentration: 100 µg/ml)

Fraction	Inhibition (%)
Methanolic fraction	42.1
CH ₂ Cl ₂ fraction	49.3
Water fraction	19.7

25

As shown in the above Table 1, the methanolic extract and CH₂Cl₂ fraction of *Angelica gigas* according to the present invention had better AChE inhibitory activity than the water fraction.

(2) Passive avoidance test

Male ICR mice weighing 25 to 30 g that had been bred with sufficient water and feed in the Experimental Animal Breeding Center of Seoul National University were supplied and adapted to the laboratory environment for 1 week to be used in this experiment.

An avoidance box (40X20X20 cm) equipped with 3 mm stainless steel rod spaced 0.5 cm apart at the bottom was divided into a light compartment and a dark compartment, and when mice placed in the light compartment entered the dark compartment, an electrical shock (0.1 mA/10 g body weight) was delivered through the stainless steel rods. The above procedure was repeated after 24 hours, and the time for which the mice stayed at the light compartment was measured and used as an index of memorizing the training of the previous day. Passive avoidance test was performed according to the method of Christensen et al. (Cholinergic 'Blockade' as a model of the cognitive deficits in Alzheimer's disease, *Brain* 115: 1681-1699, 1992). Specifically, scopolamine was dissolved in physiological saline to 1.5 mg/kg solution, and the solution was subcutaneously injected to mice 30 minutes before the training to induce amnesia. The Angelica gigas extract was intraperitoneally injected to the mice 1 hour before the scopolamine administration, and observed for its effect on the scopolamine-induced amnesia. The results are shown in the following Table 2.

Table 2: Effect of methanolic extract and CH₂Cl₂ fraction of Angelicae gigantis Radix on passive avoidance in mice with scopolamine-induced amnesia

Treatment (mg/kg)	Step-through latency (seconds)
Saline	158.8±27.6
Scopolamine 1.5	29.7±3.1
Scopolamine 1.5 + AG T 100	64.2±7.6***
+ AG C 10	48.3±9.3***
+ AG C 50	87.9±9.9***

AG T: total methanolic extract of *A. gigas*, AG C: CH₂Cl₂ fraction of *A. gigas*

The data is expressed as Mean±S.D., and the significance is ***p<0.001.

- 5 As shown in the above Table 2, the methanolic extract and CH₂Cl₂ fraction of *Angelica gigas* according to the present invention increased step-through latency in passive avoidance test to have excellent cognition-enhancing activity.

Experiment 2: Activity test of decursin and Compound 3 of Example 3

10

(1) Measurement of cholinesterase inhibitory activity

AChE inhibitory activity of decursin of the above Example 2 and Compound 3 of the above Example 3 was measured according to the method in Experiment 1.

15

- To a test tube containing a chromogen (5,5-dithiobis-2-nitrobenzoic acid) and a sample was added AChE homogenated with phosphate buffered saline (Electric eel Type V-S, Sigma), and a reaction was performed at 37 °C for 5 minutes, and thereto was added a substrate for the enzyme, acetylcholine iodide, and a reaction was further performed at 20 37 °C for 3 minutes. The above procedure was repeated with no AChE as a blank or with no sample as a control. Neostigmine bromide was added thereto to terminate the reaction, and then, the absorbance was measured at 412 nm to obtain IC₅₀ of AChE inhibition. The results are shown in the following Table 3.

25 Table 3

	IC ₅₀
Decursin (Compound 1)	4.8X10 ⁻⁴ M
Compound 3	5.1X10 ⁻⁵ M
Decursinol (Comparative Example)	2.8X10 ⁻⁵ M

As shown in the above Table 3, decursin and Compound 3 according to the present invention had better AChE inhibitory activity than decursinol (Comparative Example).

(2) Passive avoidance test

Passive avoidance test was performed according to the method of the above Experiment 1(2) to measure effects of pyranocoumarin derivatives of the present invention. Velnacrine (AChE inhibitor) was used as a positive control.

Results for decursin are shown in the following Table 4, and those for Compound 3 are in the following Table 5.

Table 4: Effects of decursin (Compound 1) and decursinol (Comparative example 1) on passive avoidance in mice with scopolamine-induced amnesia

Treatment (mg/kg)	Step-through latency (seconds)
Saline	172.0±16.0
Scopolamine 1.5	29.7±2.8
Scopolamine 1.5 + decursinol 1	52.1±8.8*
decursinol 5	54.4±10.6*
decursinol 10	43.2±7.7*
Scopolamine 1.5 + decursin 0.5	32.1±13.4
decursin 1	108.6±15.0**
decursin 5	96.5±18.2*
Scopolamine 1.5 + velnacrine 1	73.4±6.4**

The data is expressed as Mean±S.D., and the significance is *p<0.05, **p<0.01.

Table 5: Effects of Compound 3 on passive avoidance in mice with scopolamine-induced amnesia

Treatment (mg/kg)	Step-through latency (seconds)
Saline	179.7±0.6
Scopolamine 1.5	28.4±10.1
Scopolamine 1.5 + Compound 3 1	42.0±17.9

Compound 3 2	86.0±18.2 ^{***}
Compound 3 5	171.2±18.7 ^{***}

The data is expressed as Mean±S.D., and the significance is ***p<0.001.

As shown in the above Table 4, decursin showed excellent cognition-enhancing activity by remarkably increasing step-through latency in *in vivo* passive avoidance test, whereas decursinol (Comparative example) did not show such activity.

As shown in the above Table 5, Compound 3 of Example 3 according to the present invention also showed excellent cognition-enhancing activity by remarkably increasing step-through latency in *in vivo* passive avoidance test.

Hereinafter, formulation examples of the present invention will be described.

Formulation 1

Decursin	10 mg
Distilled water for injection	q. s.
pH adjusting agent	q. s.

Decursin was dissolved in distilled water for injection, and a pH adjusting agent was added thereto to the pH of about 7.6. Then, the resulting solution was adjusted to the final volume of 2 ml, and then, filled into an ampoule with the volume of 2 ml and sterilized to prepare an injectable solution.

Formulation 2

Compound 3 of Example 3	2 mg
Distilled water for injection	q. s.
pH adjusting agent	q. s.

Compound 3 was dissolved in distilled water for injection, and a pH adjusting agent was added thereto to the pH of about 7.2. Then, the resulting solution was adjusted to the final volume of 2 ml, and then, filled into an ampoule with the volume of 2 ml and
5 sterilized to prepare an injectable solution.

Formulation 3

	Methanolic extract of <i>Angelica gigas</i> of Example 1	10 mg
10	Lactic acid	100 mg
	Starch	100 mg
	Magnesium stearate	q. s.

The above ingredients were mixed and the mixture was compressed into tablets
15 according to a conventional method to manufacture tablets.

Formulation 4

	Compound 3 of Example 3	10 mg
20	Lactic acid	100 mg
	Starch	50 mg
	Magnesium stearate	q. s.

The above ingredients were mixed and the mixture was compressed into tablets
25 according a conventional method to manufacture tablets.

Formulation 5

	Decursin	5 mg
30	Lactic acid	50 mg

Starch	50 mg
Talc	2 mg
Magnesium stearate	q. s.

- 5 The above ingredients were mixed and the mixture was filled into gelatin capsules according a conventional method to manufacture capsules.

Formulation 6

10	Compound 3 of Example 3	5 mg
	Lactic acid	100 mg
	Starch	93 mg
	Talc	2 mg
	Magnesium stearate	q. s.

15

The above ingredients were mixed and the mixture was filled into gelatin capsules according a conventional method to manufacture capsules.

Formulation 7

20

Compound 3 of Example 3	50 mg
Sucrose	20 mg
Isomerized sugar	20 mg
Lemon flavor	q. s.
25 Distilled water	ad 100 ml

The above ingredients were mixed according to a conventional method to manufacture solutions, and the solution was filled into a brown bottle of 100 ml and sterilized to prepare a solution.

30

Formulation 8

	Decursin	100 mg
	Sucrose	20 mg
5	Isomerized sugar	20 mg
	Lemon flavor	q. s.
	Distilled water	ad 100 ml

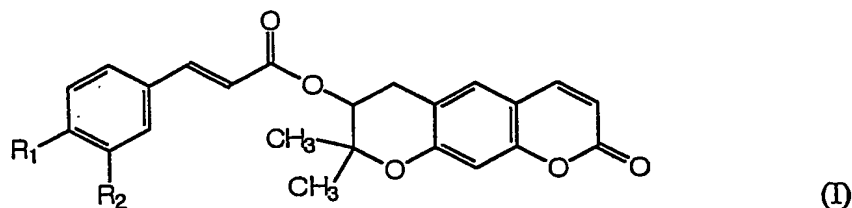
The above ingredients were mixed according to a conventional method to
10 manufacture solutions, and the solution was filled into a brown bottle of 100 ml and
sterilized to prepare a solution.

INDUSTRIAL APPLICABILITY

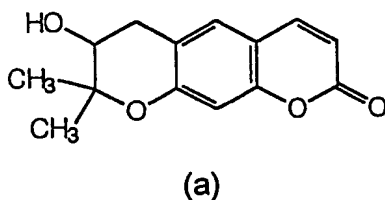
15 As can be seen from the above, the methanolic extract and CH_2Cl_2 faction of
Angelicae gigantis Radix, decursin (II), and pyranocoumarin derivatives of the above
general formula (I) have excellent cognition-enhancing activity, and can be effectively
used as an anti-dementia agent.

WHAT IS CLAIMED IS:

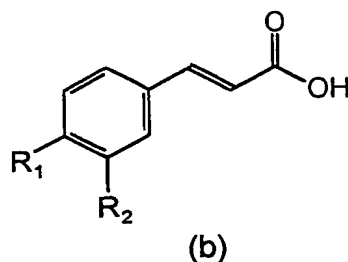
1. A pyranocoumarin derivative of the following general formula:



- 5 , wherein R₁ and R₂ each represent hydrogen or C₁₋₄alkoxy,
or a pharmaceutically acceptable salt thereof.
2. An agent for enhancing cognition, comprising the compound of the general formula (I) as defined in Claim 1 or a pharmaceutically acceptable salt thereof as an active
- 10 ingredient.
3. A process for preparing the compound of the general formula (I) as defined in Claim 1, comprising the step of esterifying decursinol of the following formula:

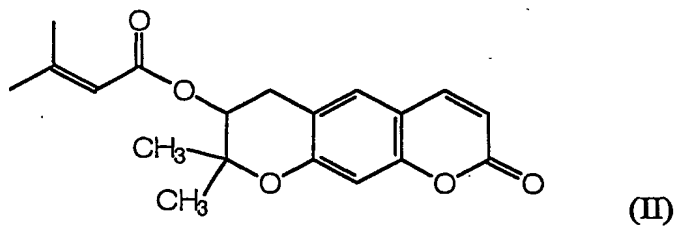


- 15 with a phenyl propanoid of the following general formula:



4. An agent for enhancing cognition, comprising decursin of the following formula:

20




or a pharmaceutically acceptable salt thereof as an active ingredient.

5. An extract of *Angelicae gigantis Radix*, comprising decursin of Claim 4.

INTERNATIONAL SEARCH REPORT

national application No.
PCT/KR02/00627

A. CLASSIFICATION OF SUBJECT MATTER IPC7 C07D 311/10 According to International Patent Classification (IPC) or to both national classification and IPC				
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC7 C07D Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Korean Patents and applications for inventions since 1975 Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) CAPLUS(STN)				
C. DOCUMENTS CONSIDERED TO BE RELEVANT				
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.		
A	Kang, So Young; Lee, Ki Yong; Sung, Sang Hyun; Park, Mi Jung; Kim, Young Choong 'Coumarins Isolated from Angelica gigas Inhibit Acetylcholinesterase Structure-Activity Relationships' Journal of Natural Products (2001), 64(5),p683-685, See the whole document	1 - 2, 4		
A	WO 2001/52841 A1(Scigenic Co., Ltd.,) 26 JULY 2001, SEE CLAIMS	1, 4		
A	WO 2000/23074 A1(Chong, Se Young; Kim, Ik Hwan; Ahn, Kyung Seop; Kim, Sang Ki) 27 APRIL 2000, SEE THE WHOLE DOCUMENT	1, 4		
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input checked="" type="checkbox"/> See patent family annex.				
<table style="width: 100%; border: none;"> <tr> <td style="width: 50%; vertical-align: top; border: none;"> * Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed </td> <td style="width: 50%; vertical-align: top; border: none;"> "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family </td> </tr> </table>			* Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family
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Date of the actual completion of the international search 29 JANUARY 2003 (29.01.2003)		Date of mailing of the international search report 29 JANUARY 2003 (29.01.2003)		
Name and mailing address of the ISA/KR  Korean Intellectual Property Office 920 Dunsan-dong, Seo-gu, Daejeon 302-701, Republic of Korea Facsimile No. 82-42-472-7140		Authorized officer WON, Ho Joon Telephone No. 82-42-481-5605		

INTERNATIONAL SEARCH REPORT

International application No.

PCT/KR02/00627

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WO 2000/23074 A1	27. 04. 2000	KR 2000026683 A KR 2000026684 A AU 9963703 A1 EP 1123097 A1	15. 05. 2000 15. 05. 2000 08. 05. 2000 16. 08. 2001